Remarks

Status of the Claims

Upon entry of the forgoing amendment, claims 57, 58, 70, 71, 79, 87 and 90-93 are pending in the application. Claim 57 and 90 are the only independent claims. Claims 57, 58, 70, 71, 79 and 87 have been amended herein. Claims 1-56, 65-69, 73, and 85 have been previously canceled, and claims 59-64, 72, 74-78, 80-84 and 85-86 are canceled herein.

Claims 57, 70, 71 and 79 have been amended to recite a pharmaceutically acceptable salt of 1-methylnicotinamide (1-MNA). Support for this amendment is found throughout the specification and in canceled claim 78.

Claim 57 has also been amended to delete reference to treatment of conditions or diseases except for hypertriglyceridemia and to include that the administering lowers said subject's plasma triglyceride level. Support for this amendment is found on page 3 line 26 to page 4, line 1 and in Example 2.

Claim 58 has been amended to recite that the treatment raises said subject's plasma HDL level. Support for this amendment is found on page 3 line 26 to page 4, line 1 and in Example 2.

Claim 87 has been amended to depend from claim 57.

New claims 90-93 have been added and are directed to a method of treating dyslipidemia. As stated at specification page 6, lines 12-14, dyslipidemia is a form of hypertriglyceridemia. Therefore, it is believed that all the new claims read on the elected species.

Additional support for new claim 90 is found, *inter alia*, in canceled claim 63, and specification page 3, lines 33-35 - page 4, line 1.

Additional support for new claim 91 is found, *inter alia*, at specification page 9, lines 17-19. Additional support for new claim 92 is found, *inter alia*, at specification page 9, lines 23-25. Additional support for new claim 93 is found, *inter alia*, at specification page 9, lines 17-22 and page 11, lines 21-23.

No new matter has been added by the amendments to the claims. Accordingly, entry of these amendments is respectively requested.

The Rejections

The first rejection under 35 U.S.C. § 103

1. At Office Action page 4, claims 57, 58, 63, 74-76, 78 and 86-89 are rejected under 35 U.S.C. § 103 as being unpatentable over Carlson *et al., Atherosclerosis 16*:359-368 (1972), in view of Gębicki *et al., Polish J. Pharmacology 55*:109-112 (2003), as evidenced by Oettgen *et al., Cancer Res. 20*:1597-1601 (1960). In view of the

cancelation of claims 63, 74-76, 78, and 86, and 88-89, this rejection is addressed by Applicants solely with regard to claims 57, 58, and 87, as amended herein.

2. Carlson is relied on, *inter alia*, as disclosing a case of massive hypertriglyceridemia with fasting triglycerides in one subject, wherein nicotinic acid or nicotinamide was administered to reduce plasma triglyceride levels to about 2-3 mmoles/L and raise the reduced levels of low-and high-density lipoproteins. Examiner states Carlson fails to disclose the specific formula I that comprises a methyl group at the 1-position, or where R is CH_3 or $N(H)CH_2OH$.

3. Gębicki is relied on, *inter alia*, as disclosing a homologue, or analog of 1-methylnicotinamide (1-MNA) as one of the two major primary metabolites of nicotinamide (NA).

4. Oettgen is relied on, *inter alia*, as disclosing charts wherein N-(hydroxymethyl)nicotinamide, instantly claimed R is $N(H)CH_2CH_3$, and 3-acetylpyridine, wherein instantly claimed R is CH_3, were equally as potent as nicotinamide, wherein instantly claimed R is NH_2, and nicotinic acid.

5. Examiner states that a skilled artisan would have envisaged the instantly claimed formula I in the treatment of hypertriglyceridemia as disclosed by Carlson in view of Gębicki, as evidence by Oettgen, and that the artisan would have been motivated to combine the art when seeking a method for treating hypertriglyceridemia wherein a compound of formula I, with an increased efficacy at a specific dose and/or a reduction

in undesirable side effects, is administered. Applicants respectfully traverse this rejection and respectfully request reconsideration.

Discussion

6. Claims 57 and 90 are the independent claims. Claim 57 has been amended to recite that the administering lowers the plasma triglyceride level in the subject who is being treated. Claim 57 has been further amended to recite a pharmaceutically acceptable salt of 1-MNA (1-methylnicotinamide) as the compound being administered. New indepenedent claim 90 contains similar language.

7. Carlson administered nicotinic acid or nictotinamide (NA) to one patient who had a "massive" hypertriglyceridemia prior to the treatment. Carlson did not administer 1-MNA to this patient *See* Carlson Abstract.

8. Applicants submit that the premise that NA is a useful therapeutic lipid lowering agent, based on Carlson's disclosure, is questionable at the very least as more fully discussed elsewhere herein. What is not in question is that there is nothing in Carlson that suggests that 1-MNA can lower triglyceride levels in a patient.

9. The deficiencies of Carlson are not cured by combining Carlson with Gębicki even as evidenced by Oettgen.

10. Gębicki discloses that 1-MNA "possesses significant anti-inflammatory properties" [bottom of page 109 to top of page 110]. Gębicki further discloses that 1-

MNA "can be used to treat a wide variety of diseases and disorders and states the use of this compound provides "certain advantages over the use of NA" (emphasis added) [top of page 110, column 1]. In other words, Gębicki discloses that 1-MNA and NA are functionally different.

11. Gębicki states:

> Based on the results presented above superior anti-inflammatory function of MNA^+ [1-MNA] over that of NA cannot be linked to scavenging properties of MNA^+. As shown in Table 1, both MNA^+ and NA cannot be regarded as effective scavengers of $O_2^{\bullet-}$ and scavenging properties against $^{\bullet}OH$ are rather medium for both compounds, however, NA is clearly more effective than MNA^+. Thus, it seems unlikely that anti-inflammatory properties of MNA^+ can be associated with its scavenging properties. (emphasis added) [page 111, first full paragraph]

In other words, Gębicki discloses and establishes that 1-MNA and NA are functionally different.

12. Gębicki further states:

> It seems to us that the superior therapeutic properties of MNA^+ over NA can be associated with the ionic character of MNA^+. We have found that MNA^+, in contrast to NA, can be bound to glycosaminoglycans. (emphasis added) [page 111, last full paragraph].

In other words, while 1-MNA and NA have different chemical structures, Gębicki discloses that they also have different ionic characteristics, which characteristics govern their activities with respect to at least certain interactions with other molecules.

13. In sum, Gębicki discloses that while 1-MNA and NA may have some broad and general features in common, they exhibit some striking differences in BOTH structure and function. These compounds therefore cannot be considered to be

interchangeable in any way, as the Examiner seems to assert, absent empirical evidence to the contrary. Such empirical evidence is nowhere to be found in either of Carlson or Gębicki.

14. Examiner allows that Gębicki does not disclose 1-MNA as a treatment of a lipid profile disorder.

15. It is clear from a reading of Gębicki that Gębicki's disclosure is focused entirely on treatment of skin, and DOES NOT disclose systemic treatment using 1-MNA.

16. Oettgen reports the effect of 1-MNA and NA on the activity of 2-amino-1,3,4-thiadiazole, an anti-neoplastic compound, as evaluated in mice. Oettgen does not disclose that administration of 1-MNA affects lipid disorders.

17. When taken as a whole, Carlson discloses administration of nicotinic acid or NA to one patient with massive hypertriglyceridemia, where triglyceride levels in that patient were lowered. Gębicki teaches that 1-MNA and NA are different in a variety of respects and 1-MNA is useful for treatment of skin diseases. Oettgen teaches that 1-MNA and NA have an effect on an anti-neoplastic compound in mice. A nexus of a common mechanism of action among the effects reported in the three documents is lacking.

18. Note that Carlson's conclusion that begins in the last paragraph on page 366 not only proposes that the active agent is NAD/NADH or "some enzyme system involved in the process of removal of plasma triglycerides," but also gives scientific reasons to justify that conclusion. Thus, the artisan of ordinary skill in the art who read

Carlson, would be led to compounds such as NAD or NADH, as a possible active agent, or to the pathway for removal of plasma triglycerides, even if such artisan also read the secondary art. To reach the invention, the artisan would be forced to ignore this discussion in Carlson, but none of the secondary art gives the artisan a reason to discount Carlson's discussion. Thus, on its face, Carlson leads away from reaching the invention, and, as a result, an artisan of ordinary skill in the art would not be motivated to treat lipid disorders using 1-MNA following a reading of Carlson in combination with the secondary cited art.

19. The skilled artisan would also not be motivated to treat lipid disorders using 1-MNA upon reading Gębicki. Gębicki provides evidence in support of the differences between 1-MNA and NA, not their similarities. Therefore, the Examiner's proposition that a *prima facie* case of obviousness is established by Carlson's use of NA to treat lipid disorders when combined with Gębicki fails, because Gębicki teaches that 1-MNA and NA are different. Moreover, Gębicki promotes 1-MNA to treat skin and discloses nothing of its use in treating lipid profile disorders. Oettgen adds nothing to Gębicki, and therefore adds nothing to Carlson, in view of Gębicki.

20. In fact, at the time when the present invention was made, it was known in the art that NA did not have hypolipidemic activity. For example, an article published in 2003 states:

> "nicotinamide, unlike nicotinic acid, produces no alteration in lipoprotein profiles."

See p. 9874, left column, Wise *et al.*, *The Journal of Biological Chemistry*, vol. 278, No. 11, 9869-9874 (2003), (submitted herewith as Fifth Supplemental IDS document NPL10) (hereafter "Wise"). Thus, the scientific statement upon which Examiner bases his legal conclusion, that the claimed invention is obvious because NA, a structurally related compound and/or a drug of which 1-MNA is a major metabolite, was allegedly known to change lipoprotein profile, is contradicted by what was known in the art.

21. The art continued to knowledge that NA does not have hypolipidemic activity is also evidenced in post filing journal publications. For example, in an article published in *The Journal of Clinical Investigation*, the author states "[i]mportantly, nicotinamide, which does not alter lipoprotein profiles . . . ." *See* p. 3400, Pike N., *The Journal of Clinical Investigation*, vol. 115, No. 12, pp. 3400-3403 (2005), (submitted herewith as Fifth Supplemental IDS document NPL8) (hereafter "Pike").

22. Because it was known at the time when the invention was made (and thereafter) that NA does not change lipoprotein profiles, Examiner's legal conclusion of obviousness is based on erroneous assumptions contradictory to what was known in the art.

23. Applicants have demonstrated that 1-MNA can lower plasma triglyceride and level and increase plasma HDL level. *See* Specification at page 3, line 26 to page 4, line 1 and Example 2.

24. Examiner acknowledges that neither Gębicki nor Oettgen mentions the activity of the compounds recited in the instant claims with respect to lipid profile.

However, Examiner contends that since Gębicki shows that 1-methylnicotinamide (MNA^+), a metabolite of NA, may be used to treat certain skin diseases and may have certain desirable properties for skin treatments, and Oettgen mentions that the compounds of Formula I of instant claims have similar antileukemic activities as does NA, a skilled artisan would have envisaged a method of treating lipid profile disorders using MNA^+ based on Carlson, Gębicki and Oettgen. *See* Office action, p. 9-10 and 12. Applicants respectfully disagree and respectfully request reconsideration.

25. Skin disorders, leukemia treatments, and lipid profile disorders are completely different targets and diseases. There is no nexus between the mechanism of action used to treat skin diseases, and the mechanism of action that interfers with an antileukemic activity of a compound, and treatment of the conditions or diseases recited in the claims. Given the lack of a nexus, and as it was known at the time of the invention that NA does not change lipid profiles, the combination of cited art does not establish a rationale for an artisan of ordinary skill in the art to extrapolate the cited art, including the combination of based on Gębicki and Oettgen, as alleged by the Examiner, to Applicants' claimed methods to use 1-MNA in a method of treating lipid profile disorders such as hypertriglyceridemia and dyslipidemia without resort to Applicants' disclosure in the instant application. Examiner paints with too broad a brush in arriving at the conclusion in Office action paragraph 23.

26. Based on the above, the claimed invention is not obvious over Carlson, in view of Gębicki as evidenced by Oettgen, when each reference is considered either alone

or in combination. Withdrawal of this rejection is believed proper, and is respectfully requested.

Carlson - 2005 - Additional support of non-obviousness of the present claims

27. Applicants submit herewith a review article, L. A. Carlson, *Journal of Internal Medicine* 2005: 258: 94-114 (Fifth Supplemental IDS document NPL5) (hereinafter "Carlson 2005"). The author of the article, L. A. Carlson, appears to be the same as of Carlson, which has been cited by the Examiner in the instant Office action. This article, published in 2005, reviews what has been known about nicotinic acid and in several instances, compares its properties with that of NA. Applicants draw the Examiner's attention to the following points:

- Altschul et al. reported [in 1955] that nicotinic acid in gram doses lowered plasma cholesterol in normal as well as hypercholesterolaemic subjects. Of considerable interest is that nicotinamide did not affect the plasma lipid levels. This is a remarkable observation as both nicotinic acid and nicotinamide, chemically quite alike, are nutritionally equivalent and known as vitamin B3. . . . The unexpected difference between nicotinic acid and nicotinamide may be due to the fact that while nicotinic acid is a powerful inhibitor of fat-mobilizing lipolysis in adipose tissue, this property is not shared by nicotinamide. *See* Carlson 2005, p. 94, col. 2.

- [In a trial conducted in 1959, nicotinic acid was found to decrease cholesterol level.] In this trial it was once again shown that nicotinamide in high doses did not lower plasma cholesterol. *See* Carlson 2005, p. 95, col. 2.

- [Several articles published in 2001 and 2003 indicate the presence of a high-affinity receptor for nicotinic acid, and such a receptor may represent a mechanism for the rapid uptake of nicotinic acid in adipose tissue and its preferential distribution and accumulation in this tissue.] Of considerable interest is that nicotinamide, which does not share the lipid metabolic effects of nicotinic acid, is not bound by this receptor. *See* Carlson 2005, p. 97, col. 2.

28. These facts, as reviewed in Carlson 2005, have been known in the art since the 1950's, and again demonstrate that there was abundant evidence known in the art that not only contradicted the single case reported in Carlson cited by the Examiner, but also still did not suggest the invention. Thus, a skilled artisan would have no rationale to extrapolate the cited art, including combining the teachings of Carlson, Gębicki and Oettgen, as alleged by the Examiner.

29. In addition, it has been known that nicotinic acid has side effects which compromise its usefulness as a therapeutic lipid lowering agent. As Carlson 2005 summarizes, based on data from an article published in 1979:

- The two regularly occurring side effects with nicotinic acid are flush and the increase in uric acid in blood. . . . The intensive skin flush induced by IR nicotinic acid is the side effect which has limited its clinical use as a lipid drug. *See* Carlson 2005, p. 106, col. 2.

30. As evidenced in Carlson 2005, research has been done on nicotinic acid that revealed that its therapeutic utility as a lipid lowering drug was limited due to its unpleasant side effects.

31. Examiner further cites Patani to support the position that a skilled artisan would have modified a lead compound to make it safer and efficient. *See* Office action, p. 11. However, what is discussed in Patani does not apply to the instant claims. Note that compounds listed in Table 12 of Patani have no resemblance to the compounds recited in the instant claims and Patani discusses the thymidylate synthase inhibitory activities of those compounds (compounds 20a-20e). *See* Patani, p. 3153, left col.But, Patani started with a compound that had, at least, some activity. Even assuming Patani provides motivation to modify Patani's compounds, such motivation cannot extend to modification of NA, because the art established that NA had no activity in altering lipid profiles. Once cannot expect to start with no activity, and then impart activity.

32. Additionally, even if Patani was successful with Patani's compound, Patani's discussion is too generic and unrelated to extend to unrelated copounds or unrelated activities. Accordingly, Patani does detract from the non-obviousness of the currently claimed invention.

33. It is evident in Carlson 2005 that there has been a long felt need in the art to identify a lipid modifying medicament similar to nicotinic acid. However, the art was unsuccessful in this endeavor. As shown in the instant application, the claimed invent fulfills this need. This long felt need and absence of success by others further demonstrate the nonobviousness of the claimed invention.

34. The discussion above explains why Examiner's reasoning does not support a legal conclusion of obviousness. Applicants respectfully assert that *prima facie* obviousness is not established, or if it has been established it has been overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

The second rejection under 35 U.S.C. § 103

The rejection

35. At Office Action page 15, claims 70-72, 77, 79 and 80 are rejected under 35 U.S.C. § 103 as being unpatentable over Carlson *et al., Atherosclerosis 16*:359-368 (1972), in view of Gębicki *et al., Polish J. Pharmacology 55*:109-112 (2003), as evidenced by Oettgen *et al., Cancer Res. 20*:1597-1601 (1960), as applied above, and further in view of Bova *et al.,* WO 99/06046 (herein "Bova"), and Mathias, U.S. Patent No. 7,153,870 B2 (herein "Mathias").

36. In view of the cancelation of claims 72, 77 and 80 herein, this rejection is addressed solely with regard to claims 70, 71 and 79, as amended herein.

37. Bova is relied on as disclosing a method for altering lipids in an individual without causing drug-induced hepatotoxicity, myopathy or rhabdomyolysis, wherein the method comprises administering to the individual once per day a single dose of a pharmaceutical combination comprising an effective lipid-altering amount of an HMG-CoA reductase inhibitor, and a cardiovascular agent.

38. Examiner states that a skilled artisan would have envisaged the instantly claimed method of treating hypertriglyceridemia, administering a quaternary pyridinium salt of formula I in combination with a cardiovascular agent as disclosed by Bova, through customary routes, i.e., oral, parenteral and inhalation, known to one of ordinary skill, as disclosed by Mathias. Examiner states that one of ordinary skill would have been motivated to combine the teachings of the aforementioned documents when seeking a combination therapy for the treatment of hypertriglyceridemia and that it would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention. Applicants respectfully traverse this rejection.

Discussion

39. Bova adds nothing to the combination of Carlson, Gębicki and Oettgen, which Applicants submit do not render claim 57 obvious, and therefore by extension, cannot render claims 70, 71 and 79 obvious. The mere inclusion of NA among a list of compounds that can be used in a combination with other compounds cannot confer obviousness on these claims.

40. Mathias disclose different modes of administration of NA derivatives that are not related in any manner to 1-MNA. Therefore, Mathias cannot correct the defects in the combination of the cited references.

41. The Examiner's reasoning does not support a legal conclusion of obviousness. Accordingly, a *prima facie* case for obviousness is not established. Withdrawal of this rejection is proper, and is respectfully requested.

The provisional rejections for obviousness type double patenting

42. At Office action page 19, claims 57, 58, 63, 70, 75, 78, 80 and 86-89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 8 of copending application no. 11/874,627. Applicants respectfully traverse this rejection.

43. In view of the cancelation of claims 63, 75, 78, 80, 86, 88 and 89, this rejection is addressed solely with regard to claims 57, 58, 70, and 87, as amended herein.

44. The filing date of 11/874,627 (October 18, 2007) is after Applicants' PCT filing date of January 7, 2005.

45. Additionally, a preliminary amendment was filed in 11/874,627 on November 10, 2009, in which the subject matter of claim 2, which is not part of this OTDP rejection, was incorporated into claim 1. Thus, claim 1 in 11/874,627 has been amended in a manner that removes it from this rejection.

46. Claims 5, 6 and 8 of the '627 application depend from amended claim 1. Since amended claim 1 has been removed from this rejection, it is believed that each of claims 5, 6 or 8 still have also been removed.

47. Therefore, it is believed that this rejection is now moot and can be withdrawn.

Conclusion

It is respectfully believed that a full and complete reply to the Office action has been made and that this application is now in condition for examination. Early notice to this effect is respectfully requested.

Respectfully submitted,

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